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Luitpold Pharmaceuticals, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

LUITPOLD PHARMACEUTICALS, INC.,

Plaintiff,

v.

AMNEAL PHARMACEUTICALS, LLC, AMNEAL HOLDINGS, LLC, AMNEAL PHARMACEUTICALS HOLDING COMPANY, LLC, AMNEAL PHARMACEUTICALS OF NEW YORK, LLC, and AMNEAL PHARMACEUTICALS CO. INDIA PRIVATE LIMITED,

Defendants;

RECORDATI IRELAND LIMITED, an Irish company,

Defendant Patent Owner.

Civil Action No. _____

Hon. _____, U.S.D.J.

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Luitpold Pharmaceuticals, Inc. ("Luitpold"), by its undersigned attorneys, brings this Complaint and action for patent infringement against Amneal Pharmaceuticals, LLC ("Amneal Pharma"), Amneal Holdings, LLC ("Amneal Holdings"), Amneal Pharmaceuticals Holding Company, LLC ("Amneal Pharmaceutical Holding"), Amneal Pharmaceuticals of New York, LLC ("Amneal NY"), and Amneal Pharmaceuticals Co. India Private Limited ("Amneal India") (collectively "the Amneal Defendants"), and hereby alleges as follows:

THE PARTIES

1. Plaintiff Luitpold Pharmaceuticals, Inc. is a corporation organized under the laws of the State of New York and has its principal place of business at One Luitpold Drive, Shirley, New York, 11967.

2. On information and belief, Amneal Pharma is a limited liability company organized under the laws of the State of Delaware, having a principal place of business at 440 U.S. Highway 22 East, Suite 104, Bridgewater, New Jersey, 08807, and is the parent corporation of Amneal NY and Amneal India. Amneal Pharma is in the business of, among other things, manufacturing and marketing generic copies of branded pharmaceutical products throughout the United States and this District.

3. On information and belief, Amneal Holdings is a corporation organized under the laws of the State of Delaware, and is the parent corporation of Amneal Pharma. Amneal Holdings is in the business of, among other things, manufacturing and marketing generic copies of branded pharmaceutical products throughout the United States including this District.

4. On information and belief, Amneal Pharmaceutical Holding is a corporation organized under the laws of the State of Delaware, and is the parent corporation of Amneal Pharma. Amneal Pharmaceutical Holding is in the business of, among other things,

manufacturing and marketing generic copies of branded pharmaceutical products throughout the United States including this District.

5. On information and belief, Amneal NY is a corporation organized under the laws of the State of Delaware, having a principal place of business at 85 Adams Avenue, Hauppage, New York, 11788, and is a subsidiary of Amneal Pharma. Amneal NY is in the business of, among other things, manufacturing and marketing generic copies of branded pharmaceutical products throughout the United States including this District.

6. On information and belief, Amneal India is an Indian corporation having a principal place of business at 882/1-871, Rajoda Village, Near Hotel Kankavati, Bavla Taluka, Ahmedabad-38220, Gujurat, India, and is a subsidiary of Amneal Pharma. Amneal India is in the business of, among other things, manufacturing and marketing generic copies of branded pharmaceutical products throughout the United States including this District.

7. On information and belief, Amneal Pharma, Amneal Holdings, Amneal Pharmaceutical Holding, Amneal NY and Amneal India hold themselves out as a unitary entity for purposes of manufacturing, marketing, selling and distributing generic pharmaceutical products.

8. Defendant patent owner Recordati Ireland Limited ("Recordati") is a company organized under the laws of the Republic of Ireland and has its principal place of business at Raheens East, Ringaskiddy, Cork County, Ireland.

NATURE OF THE ACTION

9. This is an action for infringement of United States Patent Number 6,333,044 ("the '044 patent"), arising under the United States patent laws, Title 35, United States Code, §§ 100 *et seq.*, including 35 U.S.C. §§ 271 and 281. This action relates to Amneal Pharma's filing of an Abbreviated New Drug Application ("ANDA") under Section 505(j) of the Federal Food, Drug

and Cosmetic Act ("the Act"), 21 U.S.C. §355(j) seeking U.S. Food and Drug Administration ("FDA") approval to market a generic pharmaceutical product.

JURISDICTION AND VENUE

10. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

11. This Court has personal jurisdiction over Amneal Pharma because Amneal Pharma resides in this District and it has purposely availed itself of the benefits and protections of the laws of New Jersey such that it should reasonably anticipate being haled into Court here. In addition, on information and belief, Amneal Pharma has had continuous and systematic contacts with this judicial district, including: (1) being registered to do business in New Jersey, (2) having its headquarters in New Jersey, (3) having branches of business in New Jersey, (4) conducting business in New Jersey, (5) directly, or indirectly, manufacturing, marketing, selling, and distributing generic drugs throughout the United States and in this judicial district, (6) purposely conducting and continuing to conduct business in this judicial district, and (7) the fact that this judicial district is a likely destination of Amneal Pharma's generic products. In addition, Amneal Pharma has a past practice of consenting to personal jurisdiction in this judicial district for other patent litigation matters. Thus, Amneal Pharma is subject to general jurisdiction in New Jersey.

12. This Court has personal jurisdiction over Amneal Holdings because Amneal Holdings has purposely availed itself of the benefits and protections of the laws of New Jersey such that it should reasonably anticipate being haled into Court here. In addition, on information and belief, Amneal Holdings has had continuous and systematic contacts with this judicial district, including: (1) engaging in the business of manufacturing, marketing, importing, selling and distributing pharmaceutical drug products, including generic drug products within this

judicial district, (2) directly or indirectly, in partnership and agency with its subsidiary Amneal Pharma, conducting business within the judicial district, and (3) directly or indirectly, and in partnership and agency with its subsidiary Amneal Pharma, manufacturing, marketing, selling and distributing generic drugs throughout the United States and in this judicial district. Thus, Amneal Holdings is subject to general jurisdiction in New Jersey.

13. This Court has personal jurisdiction over Amneal Pharmaceutical Holding because Amneal Pharmaceutical Holding has purposely availed itself of the benefits and protections of the laws of New Jersey such that it should reasonably anticipate being haled into Court here. In addition, on information and belief, Amneal Pharmaceutical Holding has had continuous and systematic contacts with this judicial district, including: (1) engaging in the business of manufacturing, marketing, importing, selling and distributing pharmaceutical drug products, including generic drug products within this judicial district, (2) directly or indirectly, in partnership and agency with its subsidiary Amneal Pharma, conducting business within the judicial district, and (3) directly or indirectly, and in partnership and agency with its subsidiary Amneal Pharma, manufacturing, marketing, selling and distributing generic drugs throughout the United States and in this judicial district. Thus, Amneal Pharmaceutical Holding is subject to general jurisdiction in New Jersey.

14. This Court has personal jurisdiction over Amneal NY because Amneal NY has purposely availed itself of the benefits and protections of the laws of New Jersey such that it should reasonably anticipate being haled into Court here. In addition, on information and belief, Amneal NY has had continuous and systematic contacts with this judicial district, including: (1) engaging in the business of manufacturing, marketing, importing, selling and distributing pharmaceutical drug products, including generic drug products within this judicial district, (2) directly or indirectly, in partnership and agency with its parent corporation Amneal Pharma,

conducting business within the judicial district, and (3) directly or indirectly, and in partnership and agency with its parent corporation Amneal Pharma, manufacturing, marketing, selling and distributing generic drugs throughout the United States and in this judicial district. Thus, Amneal NY is subject to general jurisdiction in New Jersey.

15. This Court has personal jurisdiction over Amneal India because Amneal India has purposely availed itself of the benefits and protections of the laws of New Jersey such that it should reasonably anticipate being haled into Court here. In addition, on information and belief, Amneal India has had continuous and systematic contacts with this judicial district, including: (1) engaging in the business of manufacturing, marketing, importing, selling and distributing pharmaceutical drug products, including generic drug products within this judicial district, (2) directly or indirectly, in partnership and agency with its parent corporation Amneal Pharma, conducting business within the judicial district, and (3) directly or indirectly, and in partnership and agency with its parent corporation Amneal Pharma, manufacturing, marketing, selling and distributing generic drugs throughout the United States and in this judicial district. Thus, Amneal India is subject to general jurisdiction in New Jersey.

16. Recordati is named as a party to this litigation as a defendant patent owner. Recordati is the lawful assignee of all right, title and interest in the '044 patent and, as detailed below, has granted an exclusive license to practice the '044 patent. The exclusive license and all rights thereunder are held by Luitpold. As a result, Luitpold has the right and standing to enforce the '044 patent and to bring this action. Further, Recordati has an interest in the outcome of this litigation, is subject to personal jurisdiction in this Court, and is a proper party to this action, as a plaintiff, defendant, or involuntary plaintiff, whichever designation is deemed appropriate by the Court.

17. Recordati has acknowledged and does not dispute that Luitpold holds an exclusive license to the '044 patent and has the exclusive right to enforce the '044 patent against the Amneal Defendants in the United States and to bring the present lawsuit.

18. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391(b) and (c), and 28 U.S.C. § 1400(b).

THE '044 PATENT

19. Luitpold holds an approved New Drug Application ("NDA"), No. 22-382, by which the FDA granted approval under Section 505(a) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(a), for Ketorolac Tromethamine Nasal Spray, 15.75 mg/spray. The Ketorolac Tromethamine Nasal Spray described in NDA No. 22-382 is marketed and sold by Luitpold in the United States under the trademark SPRIX®.

20. Recordati is the owner of the '044 patent.

21. The '044 patent was duly and legally issued on December 25, 2001. A true and correct copy of the '044 patent is attached hereto as Exhibit A.

22. The '044 patent was assigned by the inventors to Recordati, S.A. Chemical and Pharmaceutical Company, which in 2007 assigned it to Recordati. Thus, Recordati is the lawful assignee of the '044 patent.

23. On or about November 23, 2000, Roxro Pharma, Inc. or its predecessor-in-interest (hereinafter "Roxro") entered into an exclusive license agreement with Recordati or its predecessor-in-interest to the '044 patent, wherein it received an exclusive license to U.S. patent rights relating to the "intranasal formulations of the compound known as Ketorolac as described in Patent Application US 08/383707, filed February 1, 1995," which became the '044 patent. The rights under that exclusive license include, but are not limited to, the right to pursue any infringement claims against infringers of the '044 patent.

24. In December 2010, Luitpold acquired Roxro. Roxro has assigned its rights in and to its exclusive license to the '044 patent to Luitpold such that Luitpold is now the exclusive licensee of the '044 patent.

25. Pursuant to 21 U.S.C. § 355(b)(1) and applicable FDA regulations, the '044 patent is listed in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), with respect to SPRIX®.

COUNT ONE

INFRINGEMENT OF THE '044 PATENT
(AMNEAL PHARMA)

26. Luitpold realleges and incorporates by reference paragraphs 1 through 25 as if fully set forth herein.

27. Amneal Pharma submitted an ANDA (No. 204113) to the FDA under the provisions of 21 U.S.C. § 355(j) seeking approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of generic ketorolac tromethamine 15.75 mg/nasal spray (hereinafter referred to as "Amneal's ANDA product").

28. Amneal Pharma submitted its ANDA to the FDA for the purpose of obtaining approval to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's ANDA product prior to expiration of the '044 patent.

29. The relevant statute (21 U.S.C. § 355(j)(2)(B)(iv)(II)) requires that a notice of the paragraph IV certification ("Notice Letter") "include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed." The FDA's rules and regulations (21 C.F.R. § 314.95(c)(6)(ii)) further require that the detailed statement include "[f]or each claim of a patent alleged to be invalid or unenforceable, a full and detailed explanation of the grounds supporting the allegation."

30. On or about June 28, 2012, Amneal Pharma sent to Luitpold a Notice Letter, purporting to comply with the provisions of 21 U.S.C. § 355(j)(2)(B)(iv)(II) and the FDA regulations relating thereto.

31. Amneal Pharma made a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that, in its opinion and to the best of its knowledge, Amneal's ANDA product will not directly or indirectly infringe claims 4, 8, 10, 35 and 50 of the '044 patent, either literally or under the doctrine of equivalents. Amneal Pharma did not allege in the Amneal Notice Letter that the Amneal Product will not infringe claims 1-3, 5-7, 9, 11-34, 36-49 and 51 of the '044 Patent.

32. Amneal Pharma also alleged in the Amneal Notice Letter that claims 1-3, 5-7, 9, 11-34, 36-49 and 51 of the '044 Patent are invalid for obviousness under 35 U.S.C. § 103. Amneal Pharma did not allege in the Amneal Notice Letter that claims 4, 8, 10, 35 and 50 of the '044 Patent are invalid.

33. The opinions set forth in the Amneal Notice Letter that the '044 patent is not infringed and is invalid due to obviousness and other potential, unnamed theories, are devoid of an objective, good faith basis in either the facts or law. Amneal Pharma's Paragraph IV certification is a wholly unjustified infringement of the '044 patent.

34. By filing its ANDA under 21 U.S.C. § 355(j) for the purpose of obtaining approval to engage in the commercial manufacture, use, or sale of the Amneal's ANDA product before expiration of the '044 patent, Amneal Pharma has committed an act of infringement under 35 U.S.C. § 271(e)(2). Further, unless enjoined by this Court, Amneal Pharma, upon FDA approval of Amneal's ANDA, will infringe the '044 patent by making, using, offering to sell, selling and/or importing Amneal's ANDA product in the United States.

35. Amneal Pharma's method of manufacturing Amneal's ANDA product will infringe the '044 Patent, either literally or under the doctrine of equivalents, violating 35 U.S.C. §

271(a), (b) and (c).

36. Amneal Pharma's manufacturing, marketing, offering for sale, sale, and/or importation for sale of Amneal's ANDA product will induce the infringement of, and/or contributorily infringe, one or more claims of the '044 patent that teach a method in connection with ketorolac tromethamine nasal spray. This will occur at Amneal Pharma's active behest, and with its specific intent, knowledge and encouragement. On information and belief, Amneal Pharma will actively induce, encourage, aid, abet, and/or contribute to, infringement of one or more claims of the '044 patent with the knowledge that it is in contravention of Luitpold's rights under the '044 patent.

37. On information and belief, when Amneal Pharma filed its ANDA, it was aware of the '044 patent and that the filing of its ANDA with the request for its approval prior to the expiration date of the '044 patent was an act of infringement.

38. Amneal Pharma has violated its duty of care to avoid the known patent rights of the '044 patent.

39. There is a justiciable controversy between the parties hereto as to infringement and validity of certain claims of the '044 patent.

40. Luitpold is entitled to the relief provided by 35 U.S.C. § 271(e)(4), including an Order of this Court that the effective date of any approval of the aforementioned ANDA relating to Amneal's ANDA product be a date which is not earlier than December 25, 2018, the expiration of the '044 patent, or any later date of exclusivity to which Luitpold is or becomes entitled. Further, Luitpold is entitled to an award of damages for any commercial manufacture, use, offer for sale, sale, and/or importation of Amneal's ANDA product, and any act committed by Amneal with respect to the subject matter claimed in the '044 patent, which act is not within the limited exclusions of 35 U.S.C. § 271(e)(1).

41. On information and belief, prior to filing ANDA No. 22-382, the Amneal Defendants were aware of the existence of the '044 patent, and, were aware that the filing of ANDA No. 22-382, including a certification pursuant to 21 U.S.C. § 355(j)(A)(vii)(IV) with respect to the '044 patent, infringed that patent.

42. This is an exceptional case, and Luitpold is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

43. Luitpold will be substantially and irreparably damaged and harmed if Amneal Pharma is not enjoined from infringing or actively inducing or contributing to infringement of the '044 patent. Luitpold does not have an adequate remedy at law.

COUNT TWO

INFRINGEMENT OF THE '044 PATENT (AMNEAL HOLDINGS)

44. Luitpold realleges and incorporates by reference paragraphs 1 through 43 as if fully set forth herein.

45. On information and belief, Amneal Holdings initiates, directs and controls the activities of its subsidiary company, Amneal Pharma, with regard to ANDA No. 22-382, and Amneal's ANDA product.

46. On information and belief, Amneal Holdings, through Amneal Pharma as its agent, initiated, directed and controlled preparation and filing of ANDA No. 22-382 with the FDA.

47. On information and belief, Amneal Holdings has infringed the '044 patent under 35 U.S.C. § 271(e)(2)(A) by initiating, directing and controlling the preparation and filing of ANDA No. 22-382.

48. On information and belief, in the event that the FDA approves ANDA No. 22-382, Amneal Holdings stands to benefit directly from such approval by being able to commercially manufacture and distribute Amneal's ANDA product.

49. Amneal's ANDA product for which Amneal Holdings, through Amneal Pharma as its agent, seeks approval under ANDA No. 22-382, will infringe one or more claims of the '044 patent under 35 U.S.C. § 271(a).

50. The commercial manufacture, use, offer for sale, sale, and/or importation into the United States, by Amneal Holdings of Amneal's ANDA product directly or indirectly infringe one or more claims of the '044 patent under 35 U.S.C. § 271(a), (b) or (c).

51. The manufacture of Amneal's ANDA product by Amneal Holdings will infringe the '044 Patent, either literally or under the doctrine of equivalents, violating 35 U.S.C. § 271(a), (b) and (c).

52. Luitpold is entitled to full relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of ANDA No. 22-382 be a date that is not earlier than the later of December 25, 2018, the expiration of the '044 patent, or the expiration of any other exclusivity to which Luitpold is or becomes entitled.

53. On information and belief, prior to filing ANDA No. 22-382, the Amneal Defendants were aware of the existence of the '044 patent, and, were aware that the filing of ANDA No. 22-382, including a certification pursuant to 21 U.S.C. § 355(j)(A)(vii)(IV) with respect to the '044 patent, infringed that patent.

54. This is an exceptional case, and Luitpold is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

55. Luitpold will be substantially and irreparably damaged and harmed if Amneal Holdings is not enjoined from infringing or actively inducing or contributing to infringement of the '044 patent. Luitpold does not have an adequate remedy at law.

COUNT THREE

INFRINGEMENT OF THE '044 PATENT
(AMNEAL PHARMACEUTICAL HOLDING)

56. Luitpold realleges and incorporates by reference paragraphs 1 through 55 as if fully set forth herein.

57. On information and belief, Amneal Pharmaceutical Holding initiates, directs and controls the activities of its subsidiary company, Amneal Pharma, with regard to ANDA No. 22-382, and Amneal's ANDA product.

58. On information and belief, Amneal Pharmaceutical Holding, through Amneal Pharma as its agent, initiated, directed and controlled preparation and filing of ANDA No. 22-382 with the FDA.

59. On information and belief, Amneal Pharmaceutical Holding has infringed the '044 patent under 35 U.S.C. § 271(e)(2)(A) by initiating, directing and controlling the preparation and filing of ANDA No. 22-382.

60. On information and belief, in the event that the FDA approves ANDA No. 22-382, Amneal Pharmaceutical Holding stands to benefit directly from such approval by being able to commercially manufacture and distribute Amneal's ANDA product.

61. Amneal's ANDA product for which Amneal Pharmaceutical Holding, through Amneal Pharma as its agent, seeks approval under ANDA No. 22-382, will infringe one or more claims of the '044 patent under 35 U.S.C. § 271(a).

62. The commercial manufacture, use, offer for sale, sale, and/or importation into the United States, by Amneal Pharmaceutical Holding of Amneal's ANDA product directly or indirectly infringe one or more claims of the '044 patent under 35 U.S.C. § 271(a), (b) or (c).

63. The manufacture of Amneal's ANDA product by Amneal Pharmaceutical Holding will infringe the '044 Patent, either literally or under the doctrine of equivalents, violating 35 U.S.C. § 271(a), (b) and (c).

64. Luitpold is entitled to full relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of ANDA No. 22-382 be a date that is not earlier than the later of December 25, 2018, the expiration of the '044 patent, or the expiration of any other exclusivity to which Luitpold is or becomes entitled.

65. On information and belief, prior to filing ANDA No. 22-382, the Amneal Defendants were aware of the existence of the '044 patent, and, were aware that the filing of ANDA No. 22-382, including a certification pursuant to 21 U.S.C. § 355(j)(A)(vii)(IV) with respect to the '044 patent, infringed that patent.

66. This is an exceptional case, and Luitpold is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

67. Luitpold will be substantially and irreparably damaged and harmed if Amneal Pharmaceutical Holding is not enjoined from infringing or actively inducing or contributing to infringement of the '044 patent. Luitpold does not have an adequate remedy at law.

COUNT FOUR

INFRINGEMENT OF THE '044 PATENT (AMNEAL NY)

68. Luitpold realleges and incorporates by reference paragraphs 1 through 67 as if fully set forth herein.

69. On information and belief, Amneal Pharma initiates, directs and controls the activities of its subsidiary company, Amneal NY, with regard to ANDA No. 22-382, and Amneal's ANDA product.

70. On information and belief, Amneal NY, under the control of Amneal Pharma, was involved with the preparation and filing of ANDA No. 22-382 with the FDA.

71. On information and belief, Amneal NY has infringed the '044 patent under 35 U.S.C. § 271(e)(2)(A) by its involvement with the preparation and filing of ANDA No. 22-382.

72. On information and belief, in the event that the FDA approves ANDA No. 22-382, Amneal NY stands to benefit directly from such approval by being able to commercially manufacture and distribute Amneal's ANDA product.

73. The commercial manufacture, use, offer for sale, sale, and/or importation into the United States, of Amneal's ANDA product will directly or indirectly infringe one or more claims of the '044 patent under 35 U.S.C. § 271(a), (b) or (c).

74. The manufacture of Amneal's ANDA product by Amneal NY will infringe the '044 Patent, either literally or under the doctrine of equivalents, violating 35 U.S.C. § 271(a), (b) and (c).

75. Luitpold is entitled to full relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of ANDA No. 22-382 be a date that is not earlier than the later of December 25, 2018, the expiration of the '044 patent, or the expiration of any other exclusivity to which Luitpold is or becomes entitled.

76. On information and belief, prior to filing ANDA No. 22-382, the Amneal Defendants were aware of the existence of the '044 patent, and, were aware that the filing of ANDA No. 22-382, including a certification pursuant to 21 U.S.C. § 355(j)(A)(vii)(IV) with respect to the '044 patent, infringed that patent.

77. This is an exceptional case, and Luitpold is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

78. Luitpold will be substantially and irreparably damaged and harmed if Amneal NY is not enjoined from infringing or actively inducing or contributing to infringement of the '044 patent. Luitpold does not have an adequate remedy at law.

COUNT FIVE

INFRINGEMENT OF THE '044 PATENT (AMNEAL INDIA)

79. Luitpold realleges and incorporates by reference paragraphs 1 through 78 as if fully set forth herein.

80. On information and belief, Amneal Pharma initiates, directs and controls the activities of its subsidiary company, Amneal India, with regard to ANDA No. 22-382, and Amneal's ANDA product.

81. On information and belief, Amneal India, under the control of Amneal Pharma, was involved with the preparation and filing of ANDA No. 22-382 with the FDA.

82. On information and belief, Amneal India has infringed the '044 patent under 35 U.S.C. § 271(e)(2)(A) by its involvement with the preparation and filing of ANDA No. 22-382.

83. On information and belief, in the event that the FDA approves ANDA No. 22-382, Amneal India stands to benefit directly from such approval by being able to commercially manufacture and distribute Amneal's ANDA product.

84. The commercial manufacture, use, offer for sale, sale, and/or importation into the United States, of Amneal's ANDA product will directly or indirectly infringe one or more claims of the '044 patent under 35 U.S.C. § 271(a), (b) or (c).

85. The manufacture of Amneal's ANDA product by Amneal India will infringe the '044 Patent, either literally or under the doctrine of equivalents, violating 35 U.S.C. § 271(a), (b) and (c).

86. Luitpold is entitled to full relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of ANDA No. 22-382 be a date that is not earlier than the later of December 25, 2018, the expiration of the '044 patent, or the expiration of any other exclusivity to which Luitpold is or becomes entitled.

87. On information and belief, prior to filing ANDA No. 22-382, the Amneal Defendants were aware of the existence of the '044 patent, and, were aware that the filing of ANDA No. 22-382, including a certification pursuant to 21 U.S.C. § 355(j)(A)(vii)(IV) with respect to the '044 patent, infringed that patent.

88. This is an exceptional case, and Luitpold is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

89. Luitpold will be substantially and irreparably damaged and harmed if Amneal India is not enjoined from infringing or actively inducing or contributing to infringement of the '044 patent. Luitpold does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Luitpold respectfully requests the following relief:

A. A judgment declaring that the Amneal Defendants have infringed one or more claims of the '044 patent through the submission of ANDA No. 204113 to the FDA, and that the Amneal Defendants' manufacturing, using, selling, offering for sale, and/or importation of Amneal's ANDA product will infringe one or more claims of the '044 patent;

B. A judgment declaring that the Amneal Defendants' manufacture, use, sale, offer for sale, and/or importation into the United States of Amneal's ANDA product would constitute infringement of one or more claims of the '044 patent;

C. A judgment declaring that the Amneal Defendants' manufacture, use, sale, offer for sale, and/or importation into the United States of Amneal's ANDA product would induce and/or contribute to infringement of one or more claims of the '044 patent, pursuant to 35 U.S.C. § 271(a), (b), and/or (c);

D. A judgment ordering, pursuant to 35 U.S.C. § 271(e)(4), that the effective date of any FDA approval of Amneal ANDA No. 204113 be a date which is not earlier than the expiration of the '044 patent, or any later expiration of exclusivity to which Luitpold is or becomes entitled;

E. Entry of a preliminary and permanent injunction enjoining the Amneal Defendants' and their officers, agents, servants, employees, parent corporations, subsidiaries, and affiliates, and those persons in privity or in active concert or participation with any of them, from making, using, selling, offering to sell and/or importing into the United States, Amneal's ANDA product, for which approval is sought in ANDA No. 204113, or any ketorolac tromethamine nasal spray product that infringes and/or induces and/or contributes to the infringement of the '044 patent, until expiration of that patent, or any later expiration of exclusivity to which Luitpold is or becomes entitled;

F. If the Amneal Defendants engage in the commercial manufacture, use, importation of Amneal's ANDA product or any ketorolac tromethamine nasal spray product that infringes and/or induces and/or contributes to the infringement of the '044 patent, prior to the expiration of the '044 patent or any later expiration of exclusivity to which Luitpold is or becomes entitled, a judgment awarding damages to Luitpold resulting from such infringement, together with interest;

G. A finding that this is an exceptional case, and an award of attorneys' fees in this action pursuant to 35 U.S.C. § 285;

H. An award of costs and expenses in this action; and

I. Such further and other relief as this Court determines to be just and proper.

Dated: August 10, 2012

Respectfully submitted,

RIKER DANZIG SCHERER HYLAND & PERRETTI LLP

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CERTIFICATION OF NON-ARBITRABILITY

Pursuant to Local Civil Rule 201.1(d)(1), the undersigned attorney for Plaintiff, Luitpold Pharmaceuticals, Inc., certifies that this action is not eligible for arbitration under Local Civil Rule 201.1 because the relief sought in the Complaint primarily consists of a demand for preliminary and permanent injunctive relief, as well as damages believed to be in excess of $150,000.00, exclusive of interest, costs, and any claim for punitive damages.

LOCAL CIVIL RULE 11.2 CERTIFICATION

Pursuant to Local Civil Rule 11.2, the undersigned attorney for Plaintiff, Luitpold Pharmaceuticals, Inc., certifies that, to the best of his knowledge, the matter in controversy concerning the products and patent at issue herein is not the subject of another action pending in any court or in any arbitration or administrative proceeding.

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By s/ *Robert J. Schoenberg*
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Dated: August 10, 2012

Exhibit A

US006333044B1

(12) **United States Patent**
Santus et al.

(10) **Patent No.: US 6,333,044 B1**
(45) **Date of Patent: Dec. 25, 2001**

(54) **THERAPEUTIC COMPOSITIONS FOR INTRANASAL ADMINISTRATION WHICH INCLUDE KETOROLAC®**

(75) Inventors: **Giancarlo Santus**, Milan; **Giuseppe Bottoni**, Bergamo; **Ettore Bilato**, Padua, all of (IT)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **08/383,707**

(22) Filed: **Feb. 1, 1995**

Related U.S. Application Data

(63) Continuation of application No. 07/875,700, filed on Apr. 29, 1992, now abandoned.

(30) **Foreign Application Priority Data**

Jul. 22, 1991 (IT) MI91A2024

(51) **Int. Cl.**[7] **A61K 9/14**; A61K 9/12; A61K 31/40; A01N 43/38

(52) **U.S. Cl.** **424/434**; 514/947; 514/413

(58) **Field of Search** 424/434; 514/947, 514/413

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(57) **ABSTRACT**

An analgesic/anti-inflammatory pharmaceutical dosage form which comprises an effective amount of an active ingredient selected from the group consisting of racemic 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, optically active forms thereof and pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable excipient or diluent, said dosage form being an intranasally administrable dosage form.

51 Claims, No Drawings

THERAPEUTIC COMPOSITIONS FOR INTRANASAL ADMINISTRATION WHICH INCLUDE KETOROLAC®

This is a continuation of application Ser. No. 07/875,700, filed Apr. 29, 1992 abandoned.

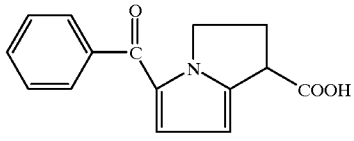
FIELD OF THE INVENTION

This invention relates to therapeutic compositions with analgesic and anti-inflammatory activity, suitable for intranasal administration, which include KETOROLAC® or its pharmaceutically acceptable salts as the active ingredient.

This invention also relates to a therapeutic method which provides for the administration of KETOROLAC® or its salts by the intranasal route.

BACKGROUND OF THE INVENTION

KETOROLAC® or 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, the formula of which is:



has been known for several years (U.S. Pat. No. 4,089,969) and is used in human therapy as an analgesic and an anti-inflammatory.

Both the racemic form and each of the dextro and levo isomers of this compound are known. Many pharmaceutically acceptable salts, the most commonly used of which is the tromethamine(2-amino-2-hydroxymethyl-1,3-propanediol) salt, are also known. Hereinafter, the name KETOROLAC® shall encompass individually or collectively the racemic mixture or either optically active compound and shall encompass the free acid as well as the tromethamine salt or any other pharmaceutically acceptable salt of any one of the foregoing.

Ample literature is available on KETOROLAC® (for instance, "KETOROLAC®—A review of its pharmacodynamic and pharmacokinetic properties and its therapeutic potential", *Drugs* 39(1): 86–109, 1990. It is described as a drug with considerably higher analgesic and anti-inflammatory activity than many other non-steroid anti-inflammatory drugs. Most significantly, it has higher analgesic activity than morphine, without the well-known side effects of the latter.

In the several pharmacological and clinical trials involving KETOROLAC® that have been conducted, this drug was administered both by the oral route and by injection (in turn, both intravenous and intramuscular). Regardless of the administration route, KETOROLAC® proved active and was found comparatively more active than the better known non-steroid drugs with analgesic and anti-inflammatory activity. However, about 10% of the patients treated (20 doses of 30 mg each administered over five days) by the intramuscular route suffered from one or more undesirable side effects such as somnolence, local (injection site) pain, sweating, nausea, headache, dizziness, vomiting, pruritus, and vasodilation.

The incidence of side effects was even higher (around 32%) in the patients treated with KETOROLAC® by the oral route for a few days. In the case of oral administration, gastrointestinal disorders (nausea, g.i. pain, dyspepsia, diarrhea, flatulence, g.i. fullness, vomiting) were noted in up to 50% of the patients in addition to side effects incident to i.m. administration.

Intravenous administration is inconvenient and is limited to the treatment of acute conditions.

On the whole, the data available to date clearly describe a drug which is very active, but still unsatisfactory from the point of view of convenience of administration and/or side effects.

SUMMARY OF THE INVENTION

We have now found that it is possible to prepare Analgesic/anti-inflammatory formulations containing KETOROLAC® as an active ingredient, which are suitable for intranasal administration and that KETOROLAC® so administered is rapidly and thoroughly absorbed, giving therapeutic effects equivalent to those obtained by the intravenous route (acute treatments) or the intramuscular or oral routes (extended or chronic treatments), without inducing severe side effects. Most important, any possibility of gastrointestinal disorders is excluded, while disorders caused by CNS stimulation are considerably reduced both in incidence (e.g. number of patients affected) and intensity.

Another aspect of the present invention is directed to a therapeutic method for the treatment of inflammatory processes and for the therapy of pain of a traumatic or pathologic origin, which method comprises administering by the intranasal route an analgesic/anti-inflammatory amount of KETOROLAC® along with an absorption promoter and pharmaceutically acceptable diluents and/or excipients.

The new method provides for the intranasal administration of KETOROLAC® doses ranging between 0.5 and 40 mg, preferably between 5 and 30 mg, and is particularly effective in acute therapies, where a very rapid systemic delivery is required especially one not accompanied by the drawbacks of i.v. delivery (hospitalization, cost, etc.).

DETAILED DESCRIPTION OF THE INVENTION

All cited patents and literature are incorporated by reference in their entirety.

Although nasal administration to mammals (especially humans) of certain therapeutic agents is known, it is not to be presumed that all therapeutic agents can be effectively administered by this route. To the contrary, many therapeutic agents cannot be nasally administered. At present, the molecules which have proved suitable for this route of administration are still very few and consist essentially of only small peptide or hormone molecules (such as calcitonin, cerulean, β-endorphin, glucagon, horseradish peroxidase, B-interferon, oxytocin and insulin) in special formulations. The ability of drug molecules to be absorbed by the nasal mucous membranes is utterly unpredictable, as is the ability of intranasal formulations to avoid irritation of the mucous nasal membranes. In fact, mucous membrane irritation caused by the drug and/or excipient is the most common reason for which intranasal administration has not gained wider acceptance.

The new compositions according to the invention include the active ingredient in quantities ranging from 0.5 to 40 mg per dose, preferably 5 to 30 mg per dose, diluted in excipients such as humectants, isotoning agents, antioxidants, buffers and preservatives. A calcium chelating agent is also preferably included.

The intranasal formulations of the invention contain KETOROLAC® concentrations ranging from 5 to 20%,

preferably about 15% weight/volume. Of course, the selection of the particular excipients depends on the desired formulation dosage form, i.e. on whether a solution to be used in drops or as a spray (aerosol) is desired or a suspension, ointment or gel to be applied in the nasal cavity are desired. In any case, the invention make it possible to have single-dose dosage forms, which ensure application of an optimum quantity of drug.

Administration of the present intranasal formulations provides very good absolute bioavailability of KETOROLAC®, as demonstrated in tests involving rabbits. The predictive value of the rabbit model with respect to bioavailability of nasally administered KETOROLAC® in humans is art-recognized (Mroszczak, E. J. et al., *Drug Metab. Dispos.,* 15:618–626, 1987, especially Tables 1 and 3). According to the results of the rabbit tests set forth below it is extrapolated that in humans intranasal administration of a composition according to the invention in amounts ranging between 0.5 mg/kg/day and 4 mg/kg/day will generate plasma levels of KETOROLAC® within the range of 0.3–5 mg/liter of plasma.

Suitable vehicles for the formulations according to the invention include aqueous solutions containing an appropriate isotoning agent selected among those commonly used in pharmaceutics. Substances used for this purpose are, for instance, sodium chloride and glucose. The quantity of isotoning agent should impart to the vehicle (taking into account the osmotic effect of the active ingredient), an osmotic pressure similar to that of biological fluids, i.e. generally from about 150 to about 850 milliOsmoles (mOsm) preferably from about 270 to about 330 mOsm.

However, it is known that nasal mucous membranes are also capable of tolerating slightly hypertonic solutions. Should a suspension or gel be desired instead of a solution, appropriate oily or gel vehicles may be used or one or more polymeric materials may be included, which desirably should be capable of conferring bioadhesive characteristics to the vehicle.

Several polymers are used in pharmaceutics for the preparation of a gel; the following can be mentioned as nonlimiting examples: hydroxypropyl cellulose (KLUCEL®), hydroxypropyl methyl cellulose (METHOCEL®), hydroxyethyl cellulose (NATROSOL®), sodium carboxymethyl cellulose (BLANOSE®), acrylic polymers (CARBOPOL®, POLYCARBOPHIL®), gum xanthan, gum tragacanth, alginates and agar-agar.

Some of them, such as sodium carboxymethyl cellulose and acrylic polymers, have marked bioadhesive properties and are preferred if bioadhesiveness is desired.

Other formulations suitable for intranasal administration of KETOROLAC® can be obtained by adding to the aqueous vehicle polymers capable of changing the rheologic behavior of the composition in relation to the temperature. These polymers make it possible to obtain low viscosity solutions at room temperature, which can be applied for instance by nasal spray and which increase in viscosity at body temperature, yielding a viscous fluid which ensures a better and longer contact with the nasal mucous membrane. Polymers of this class include without limitation polyoxyethylene-polyoxypropylene block copolymers (POLOXAMER®).

In addition to aqueous, oil or gel vehicles, other vehicles which may be used in the compositions according to the invention comprise solvent systems containing ethyl alcohol, isopropyl alcohol, propylene glycol, polyethylene glycol, mixtures thereof or mixtures of one or more of the foregoing with water.

In any case, a pharmaceutically acceptable buffer should be present in order to create optimum pH conditions for both product stability and tolerance (pH range about 4 to about 8; preferably about 5.5 to 7.5). Suitable buffers include without limitation tris (tromethamine) buffer, phosphate buffer, etc.

Other excipients include chemical enhancers such as absorption promoters. These include chelating agents, fatty acids, bile acid salts and other surfactants, fusidic acid, lysophosphatides, cyclic peptide antibiotics, preservatives, carboxylic acids (ascorbic acid, amino acids), glycyrrhetinic acid, o-acylcarnitine. Preferred promoters are diisopropyladipate, POE(9) lauryl alcohol, sodium glycocholate and lysophosphatidyl-choline which proved to be particularly active. Finally, the new compositions according to the invention preferably contain preservatives which ensure the microbiological stability of the active ingredient. Suitable preservatives include without limitation, methyl paraoxybenzoate, propyl paraoxybenzoate, sodium benzoate, benzyl alcohol, benzalkonium chloride and chlorobutanol.

The liquid KETOROLAC® formulations, preferably in the form of solutions, may be administered in the form of drops or spray, using atomizers equipped with a mechanical valve and possibly including a propellant of a type commercially available, such as butane, N_2, Ar, CO_2, nitrous oxide, propane, dimethyl ether, chlorofluorocarbons (e.g. FREON) etc. Vehicles suitable for spray administration are water, alcohol, glycol and propylene glycol, used alone or in a mixture of two or more.

Generally, illustrative formulations will contain the following ingredients and amounts (weight/volume):

Ingredient	Broad Range (%)	Preferred Range (%)
Na_2 EDTA	0.001–1	0.05–0.1
Nipagin	0.01–2	0.05–0.25
POE (9) Lauryl alcohol	0.1–10	1–10
NaCMC (Blanose 7m8 sfd)	0.1–5	0.3–3
Carbopol 940	0.05–2	0.1–1.5
Glycerol	1–99	
Sodium glycocholate	0.05–5	0.1–1

It will be appreciated by those of ordinary skill that ingredients such as sodium carboxymethyl cellulose and Carbopol exist in many types differing in viscosity. Their amounts are to be adjusted accordingly. Different adjustments to each formulation may also be necessary including omission of some optional ingredients and addition of others. It is thus not possible to give an all-encompassing amount range for each ingredient, but the optimization of each preparation according to the invention is within the skill of the art.

Another, although not preferred, alternative for the intranasal administration of the KETOROLAC®-based compositions comprises a suspension of finely micronized active ingredient (generally from 1 to 200 micrometers, preferably from 5 to 100 micrometers) in a propellant or in an oily vehicle or in another vehicle in which the drug is not soluble. The vehicle is mixed or emulsified with the propellant. Vehicles suitable for this alternative are, for instance, vegetable and mineral oils and triglyceride mixtures. Appropriate surfactants, suspending agents and diluents suitable for use in pharmaceutics are added to these vehicles. Surfactants include without limitation sorbitan sesquioleate, sorbitanmonooleate, sorbitan trioleate (amount: between about 0.25 and about 1%); suspending agents include with-

out limitation isopropylmyristate (amount: between about 0.5 and about 1%) and colloidal silica (amount: between about 0.1 and about 0.5%); and diluents include without limitation zinc stearate (about 0.6 to about 1%).

The following examples of formulations for the intranasal administration of KETOROLAC® serve to illustrate the invention without limiting its scope.

EXAMPLE 1

Composition	%	For 10 liters
KETOROLAC ® tromethamine	5	500 g
EDTA disodium (chelating agent)	0.01	1 g
NIPAGIN (preservative)	0.1	10 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA disodium.

Stir the solution constantly to complete dissolution of the components.

Cool the obtained solution to room temperature.

Dissolve KETOROLAC® tromethamine by stirring.

Bring to volume with water.

The isotonicity of this composition was 190 mOsm but can be adjusted e.g. to 270 mOsm by the addition of 0.3% NaCl or 2.03% of glucose.

EXAMPLE 2

Composition	%	For 10 liters
KETOROLAC ® tromethamine	5	500 g
POE (9) lauryl alcohol (enhancer/promoter)	5	500 g
NIPAGIN	0.1	10 g
EDTA disodium	0.01	1 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA disodium.

Stir the solution constantly to complete dissolution, of the components.

Cool the obtained solution to room temperature.

Add POE (9) lauryl alcohol and stir to complete dissolution.

Dissolve KETOROLAC® tromethamine by stirring.

Bring to volume with water.

EXAMPLE 3

Composition	%	For 10 liters
KETOROLAC ® tromethamine	5	500 g
Sodium carboxymethyl cellulose	1	100 g
Tromethamine, q.s. to pH = 6		
NIPAGIN	0.1	10 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN.

Cool the obtained solution to room temperature.

Dissolve KETOROLAC® and continue stirring to complete dissolution of the drug.

Disperse sodium carboxymethyl cellulose in the solution stirring vigorously.

Continue stirring to complete hydration of the polymer.

Adjust the pH to the required value by suitably adding tromethamine dissolved in water.

Bring to volume with water.

EXAMPLE 4

Composition	%	For 10 liters
KETOROLAC ® tromethamine	5	500 g
NIPAGIN	0.1	10 g
EDTA disodium	0.01	1 g
CARBOPOL 940	0.1	10 g
Tromethamine, q.s. to pH = 7–7.4		
Glycerol	2	200 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 4 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA.

Cool the solution to room temperature.

Dissolve KETOROLAC® tromethamine.

Complete the dissolution of the active ingredient and adjust the pH to a value of 7.1–7.4 by adding a 5% tromethamine solution.

In a separate vessel equipped with mixer, introduce the quantity of glycerol called for in the formulation.

Introduce CARBOPOL and mix until a homogeneous dispersion in the glycerol is obtained.

Add 4 liters of purified water with vigorous stirring and continue stirring the solution to complete hydration of the polymer.

Combine the solution containing the active ingredient and the polymer solution with stirring.

If necessary, adjust the pH to the required value with the tromethamine solution.

Bring to volume with water.

EXAMPLE 5

Composition	%	For 10 liters
KETOROLAC ® tromethamine	5	500 g
LUTROL F127	17	1.7 Kg
EDTA disodium	0.01	1 g
NIPAGIN	0.1	10 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 4 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA disodium.

Cool the solution to 4° C. and then, maintaining it between 4 and 6° C. throughout the operation, gradually add Lutrol F127 with stirring.

Continue stirring to complete hydration of the polymer.
Bring the solution to room temperature.
Dissolve KETOROLAC® tromethamine.
Bring to volume with water.

EXAMPLE 6

Composition	%	For 10 liters
KETOROLAC ® tromethamine	5	500 g
Sodium carboxymethyl cellulose	2	200 g
EDTA disodium	0.01	1 g
NIPAGIN	0.1	10 g
Purified water, q.s. to	100	10 L

The procedure of Example 3 was used to make the above formulation except that no buffer was added.

EXAMPLE 7

Composition	%	For 10 liters
KETOROLAC ® tromethamine	5	500 g
LUTROL F127	15	1500 g
EDTA disodium	0.01	1 g
NIPAGIN	0.1	10 g
Purified Water, q.s. to	100	10 L

The procedure of Example 5 was used to make the above formulation.

EXAMPLE 8

Composition	%	For 10 liters
KETOROLAC ® tromethamine	5	500 g
EDTA disodium	0.01	1 g
NIPAGIN	0.1	10 g
Sodium glycocholate	0.3	30 g
Purified water, q.s. to	100	10 L

The procedure of Example 1 was used except that sodium glycocholate was dissolved with the nipagin and disodium EDTA at 80° C. in water. The isotonicity of this composition was 190 mOsm; it can be adjusted e.g. to 330 mOsm by the addition of 0.44% NaCl or 3.05% glucose.

EXAMPLE 9

Composition	%	For 10 liters
KETOROLAC ® tromethamine	5	500 g
Lutrol F127	15	1500 g
Sodium glycocholate	0.3	30 g
EDTA disodium	0.01	1 g
NIPAGIN	0.1	10 g
Purified water, q.s. to	100	10 L

The procedure of Example 5 was used except that sodium glycocholate was dissolved along with nipagin and disodium EDTA at 80° C.

EXAMPLE 10

We studied the stability of the preparations described in the Examples 1 2, 6, 7, 8 and 9. The storing conditions were 4° C., 22° C., 45° C. and 55° C. We analyzed the preparations at the beginning of the storing period and after 1, 2, 3 and 6 months. We used UV and HPLC analysis.

The parameters tested were:

content of active compound (UV and HPLC)

content of keto and hydroxy degradation products (UV and HPLC)

appearance and color (visual examination)

pH (digital pH meter)

The results are summarized in Table 1.

TABLE 1

Example	Temp. ° C.	Months	KTM (mg/ml)	Keto %	Hydroxy %	Appearance of solution	pH
1	22	0	50.1	0.8	0.3	light yellow	6.2
	45	2	50.8	0.2	0.0	yellow	6.5
	45	3	49.6	0.2	0.0	opalescent yellow	6.5
	45	6	51.4	0.4	0.0	yellow with deposit	6.5
2	22	0	49.0	0.1	0.3	light yellow	6.4
	45	2	47.7	0.4	0.0	yellow	6.8
	45	3	46.7	0.2	0.0	yellow	6.9
	45	6	47.3	1.0	0.0	yellow	7.0
6	22	0	49.6	0.1	0.4	yellow	6.0
	45	1	47.0	0.1	0.1	yellow	6.5
	45	3	48.8	0.2	0.0	yellow	6.5
	45	6	50.1	0.9	0.0	yellow with deposit	5.5
7	22	0	48.5	0.0	0.5	light yellow	6.7
	55	1	49.0	0.8	0.0	yellow gel	6.8
	55	3	47.1	1.4	1.9	orange gel	6.6
8	22	0	52.3	0.0	0.0	light yellow	6.2
	45	1	53.2	0.0	0.0	yellow	6.4
	45	3	54.3	0.5	0.0	yellow	6.5
9	22	0	48.7	0.0	0.0	light yellow	6.7
	45	1	51.7	0.0	0.0	yellow	6.8

EXAMPLE 11

We tested in vitro the thermosetting properties of some preparations (Examples 1, 2, 7, 9). We sprayed a standardized amount of every preparation to a 37° C. constant-temperature, vertical glass surface and we measured the time that the drops of preparation spent to cover 10 cm. The speed of solution in moving on the constant-temperature surface is an indicator of the thermosetting properties of the dosage form. Examples 7 and 9 gave the best results in terms of thermosetting properties.

The results are reported in Table 2.

TABLE 2

Preparation	Time to Cover 10 cm
H_2O	3 sec.
Example 1	3 sec.
Example 2	3 sec.
Example 7	12 sec.
Example 9	15 sec.

EXAMPLE 12

We studied the nasal absorption and the local tolerance of four preparations (Examples 1, 6, 8, 9) in White New Zealand rabbits (three rabbits for each experimental group plus three controls). Each rabbit received a active preparation in one nostril and its placebo in the other. Each animal received 2 mg/kg of KETOROLAC® tromethamine (KTM), twice a day for seven days and once on the eighth day. The control rabbits were treated, after seven days of nasal

administration of physiologic solution, with 2 mg/kg of KTM by intravenous route once. After the last treatment plasma samples were collected at several times and KTM plasma levels were investigated by HPLC. After the last blood sample was drawn all the animals were killed by excision of femoral arteries, after having been completely anaesthetized. Nasal turbinates, larynx and pharynx were removed and subjected to histological examinations.

Pharmacokinetic parameters are reported in Tables 3, 4, 5, 6, 7 and in FIG. 1. The local (nasal mucous) tolerance data showed good tolerance of the KETOROLAC-containing intranasal preparations with the formulation of Example 1 being the best tolerated followed by that of Example 6, Example 9 and Example 8 in that order.

TABLE 3

Control Absorption of KTM
Route of Administration: Intravenous
Administered Dose: 2 mg/kg
Plasma Concentration of KTM as ng/ml

Sampling Time (hours)	Mean	± S.D.
Basal	0	0
0.083	14510	1999
0.25	7682	2887
0.5	3884	1891
1	1703	792
2	403	167
3	120	67
5	20	7

TABLE 4

Nasal Absorption of KTM
Composition: Example 1
Route of Administration: Intranasal
Administered Dose: 2 mg/kg/administration

Sampling Time (hours)	Mean	± S.D.
Basal	18	16
0.25	2363	1035
0.5	1875	726
1	1103	490
2	593	217
3	267	55
5	121	52

TABLE 5

Nasal Absorption of KTM
Composition: Example 8
Route of Administration: Intranasal
Administered Dose: 2 mg/kg/administration

Sampling Time (hours)	Mean	± S.D.
Basal	29	22
0.25	2973	1258
0.5	2654	880
1	2246	1145
2	1121	832
3	665	444
5	427	194

TABLE 6

Nasal Absorption of KTM
Composition: Example 9
Route of Administration: Intranasal
Administered Dose: 2 mg/kg/administration

Sampling Time (hours)	Mean	± S.D.
Basal	35	17
0.25	2036	572
0.5	1663	778
1	1009	345
2	325	103
3	184	22
5	198	52

TABLE 7

Nasal Absorption of KTM
Composition: Example 6
Route of Administration: Intranasal
Dose Administered: 2 mg/kg/administration

Sampling Time (hours)	Mean	± S.D.
Basal	23	20
0.25	1872	1228
0.5	1772	1027
1	1213	619
2	616	293
3	269	96
5	133	23

From the foregoing data, the following bioavailability parameters were calculated:

TABLE 8

Formulation	i.v.	Example 1 (A)	Example 8 (B)	Example 9 (C)	Example 6 (D)
		AUC_{0-5} (h.ng/ml)			
average	7355	3237	5972	2692	3197
± S.D.	2405	1129	2973	571	976
CV (%)	32.7	34.9	49.8	21.2	30.5
		T_{max} (hours)			
average		0.25	0.42	0.33	0.33
± S.D.		0	0.14	0.14	0.14
CV (%)		0	34.6	43.3	43.3
		C_{max} (ng/ml)			
average		2363	3226	2229	1895
± S.D.		1035	1079	335	1203
CV (%)		43.8	33.4	15.0	63.5
		AUC i.n./AUC i.v.			
average		0.44	0.81	0.36	0.43

i.n. = intranasal
i.v. = intravenous

Each value is the mean of the data obtained from three animals.

The foregoing results indicate that intranasal formulations of KETOROLAC® according to the invention compare favorably with intravenous formulations in terms of absorption (Formulation B from Example 8 being the best absorbed), time to maximum plasma concentration, and maximum plasma concentration and exhibit good absolute bioavailability (especially formulation B).

EXAMPLE 13

Composition	%	For 10 Liters
KETOROLAC ® tromethamine	15	1500 g
EDTA disodium	0.01	1 g
NIPAGIN	0.2	20 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA disodium.

Stir the solution constantly to complete dissolution of the components.

Cool the obtained solution to room temperature.

Dissolve KETOROLAC® tromethamine by stirring.

Bring to volume with water.

EXAMPLE 14

Composition	%	For 10 Liters
KETOROLAC ® tromethamine	15	1500 g
EDTA disodium	0.01	1 g
NIPAGIN	0.2	20 g
Glycocholic acid	0.3	30 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 9 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA disodium.

Stir the solution constantly to complete dissolution of the components.

Cool the obtained solution to room temperature.

Dissolve KETOROLAC® tromethamine and glycocholic acid by stirring.

Bring to volume with water.

EXAMPLE 15

Composition	%	For 10 Liters
KETOROLAC ® tromethamine	15	1500 g
EDTA disodium	0.01	1 g
NIPAGIN	0.2	20 g
Glycocholic acid	0.3	30 g
Lutrol F 127	15	1500 g
Purified water, q.s. to	100	10 L

Method of Preparation

In a suitable vessel equipped with mixer and heating sleeve, introduce about 8 liters of purified water and heat to a temperature of 80° C.

Dissolve NIPAGIN and EDTA disodium.

Stir the solution to 4° C. and then, maintaining it between 4° and 6° C. throughout the operation, gradually add Lutrol F127 with stirring.

Continue stirring to complete hydration of the polymer.

Bring the solution to room temperature.

Dissolve KETOROLAC® tromethamine and glycocholic acid.

Bring to volume with water.

APPENDIX OF PRODUCT NAMES AND EXAMPLES OF COMMERCIAL SOURCES

KETROLAC TROMETHAMINE: SYNTEX IRELAND, CLARECASTLE, IRELAND

HYDROXYPROPYLCELLULOSE (KLUCEL) DOW CHEMICAL CO, MIDLAND Mich. USA

HYDROXYPROPYLMETHYLCELLULOSE (METHOCEL) DOW CHEM. CO, MIDLAND Mich.

HYDROXYETHYLCELLULOSE (NATROSOL) HERCULES INC, WILMINGTON Del. USA

SODIUM CARBOXYMETHYLCELLULOSE (BLANOSE) HERCULES INC, WILMINGTON Del.

CARBOPOL: BF GOODRICH CHEMICAL CO., CLEVELAND, Ohio, USA

POLYCARBOPHIL: BF GOODRICH CHEMICAL CO., CLEVELAND, Ohio, USA

GUM TRAGACANTH: COLONY IP. & EXP. CO., NEW YORK, N.Y., USA

GUM XANTHAN: ALDRICH CHEMIE, STANHEIM, GERMANY

SODIUM ALGINATE: EDWARD MANDELL CO., CARMEL, NEW YORK, USA

AGAR AGAR: ALDRICH CHEMIE, STANHEIM, GERMANY

POLOXAMER (LUTROL f127): BASF WYNDOTTE CORP., PARSIPPANY, N.J., USA

ETHYL ALCOHOL: EASTMAN CHEMICAL PRODUCTS INC., KINGSPORT, Tenn., USA

ISOPROPYL ALCOHOL: BAKER CHEMICAL CO., NEW YORK, N.Y., USA

PROPYLENE GLYCOL: DOW CHEMICAL CO., MIDLAND, Mich., USA

POLYETHYLENE GLYCOL: BASF WYNDOTTE CORP., PARSIPPANY, N.J., USA

DIISOPROPYLADIPATE: CRODA, GOOLE, NORTH HUMERSIDE, UK

SODIUM GLYCOCHOLATE: SIGMA CHEMICAL COMPANY, ST. LOUIS, Mo., USA

LYSOPHOSPHATIDYLCHOLINE: AMERICAN LECITHIN, LONG ISLAND, N.Y., USA

METHYLPARAOXYBENZOATE (NIPAGIN): BDH CHEMICAL LTD, POOLE, DORSET, UK

PROPYLPARAOXYBENZOATE: BDH CHEMICAL LTD, POOLE, DORSET, UK

SODIUM BENZOATE: PFIZER INC., NEW YORK, N.Y., USA.

BENZYL ALCOHOL: BDH CHEMICAL LTD, POOLE DORSET, UK

BENZALCONIUM CHLORIDE: ION PHARMACEUTICALS, COVINA, Calif., USA

CHLORBUTANOL: EASTERN CHEMICAL PRODUCTS, SMITHTOWN, N.Y. USA

EDTA DISODIUM: GRACE AND CO., LONDON, UK.

POE(9)LAURYL ALCOHOL: BASF WYNDOTTE CORP, PARSIPPANY, N.J., USA

TROMETHAMINE: FARMITALIA, MILAN, ITALY

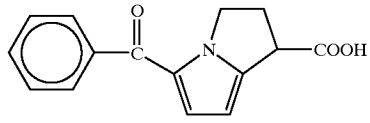
GLYCEROL: DOW CHEMICAL CO., MIDLAND, Mich., USA

SODIUM CHLORIDE: ALDRICH CHEMIE, STANHEIM, GERMANY

GLUCOSE: ROQUETTE LTD, TUNBRIDGE WELLS, KENT, UK

What is claimed is:

1. An analgesic/anti-inflammatory pharmaceutical liquid dosage form which comprises a systemically effective amount of an active ingredient selected from the group consisting of racemic 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, of the formula



optically active forms thereof and pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable excipient or diluent, said dosage form being a non-thermosetting intranasally administrable transmucosally rapidly absorbable dosage form that achieves blood levels in a host effective for analgesic or anti-inflammatory use after intranasal administration.

2. The dosage form of claim **1** comprising 0.5–40 mg of said active ingredient.

3. The dosage form of claim **1** comprising 2–20 mg of said active ingredient.

4. The dosage form of claim **1** in a single-dose form.

5. The dosage form of claim **1** comprising 5–20% of said active ingredient (weight/volume).

6. The dosage form of claim **1** in the form of a solution or suspension.

7. The dosage form of claim **1** containing 15% of said active ingredient.

8. The dosage form of claim **1** wherein said excipient comprises a bioadhesive.

9. The dosage form of claim **1** further comprising as an excipient an intranasal absorption promoter.

10. The dosage form of claim **8** wherein said promoter is selected from the group consisting of POE (9) lauryl alcohol and sodium glycocholate and lysophosphatidyl choline.

11. A method for the treatment of inflammatory processes and pain of a traumatic or pathologic origin which comprises the administration by the intranasal route of a dosage form according to claim **1**.

12. A method according to claim **11** wherein said mammal is a human and wherein said effective amount is sufficient to generate a plasma concentration of 5-benzdyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid within the range between 0.3 and 5 mg/liter of plasma.

13. The dosage form of claim **1** comprising a mucosal absorption promoter that is not a mucosal irritant.

14. A method for the treatment of inflammatory processes and pain of a traumatic or pathologic origin, which comprises the administration by the intranasal route of a dosage form comprising a systemically effective amount of the active ingredient 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid, in a racemic or optically active form or in the form of a pharmaceutically acceptable salt, said dosage form being a non-thermosetting intranasally administrable transmucosally rapidly absorbable dosage form that achieves blood levels for said active ingredient effective for analgesic or anti-inflammatory use after intranasal administration.

15. A method according to claim **14** wherein said effective amount is within the range of 0.5–40 mg.

16. A method according to claim **14** wherein said effective amount is within the range of 5–30 mg.

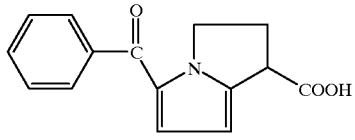
17. A method according to claim **14** wherein said effective amount is within the range of 5–20% (weight/volume).

18. A method according to claim **14** wherein said effective amount is within the range of 15% (weight/volume).

19. A method according to claim **18** wherein said dosage form comprises said active ingredient is dissolved in an aqueous liquid carrier.

20. A method according to claim **18** wherein said dosage form also comprises a mucosal adsorption promoter that is not a mucosal irritant.

21. An analgesic/anti-inflammatory pharmaceutical liquid dosage form which comprises a systemically effective amount for a human of an active ingredient selected from the group consisting of racemic 5-benzoyl-2,3-dihyro-1H-pyrrolizine-1-carboxylic acid, of the formula



optically active forms thereof and pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable excipient or diluent, said dosage form being an intranasally administrable transmucosally rapidly absorbable dosage form that achieves blood levels in a host effective for analgesic or anti-inflammatory use after intranasal administration, wherein the dosage form is free of polymers providing a low viscosity composition at room temperature but an increased viscosity composition at body temperature.

22. The dosage form of claim **21** in the form of a solution.

23. The dosage form of claim **21** in combination with a container suitable for delivering a spray of the liquid dosage form.

24. The dosage form of claim **21** comprising about 5–20% of said active ingredient (weight/volume).

25. The dosage form of claim **24** containing about 15% of said active ingredient (weight/volume).

26. The liquid dosage form of claim **21**, wherein the active ingredient is a pharmaceutically acceptable salt.

27. The liquid dosage form of claim **26**, wherein the active ingredient is ketorolac tromethamine and the diluent is water.

28. The dosage form of claim **27** in the form of a solution.

29. The dosage form of claim **28** comprising about 5–20% of ketorolac tromethamine (weight/volume).

30. The dosage form of claim **29** containing about 15% of ketorolac tromethamine (weight/volume).

31. The dosage form of claim **27** consisting essentially of an aqueous solution of ketorolac tromethamine optionally containing at least one additive chosen from a humectant, isotoning agent, antioxidant, buffer, preservative, and chelating agent.

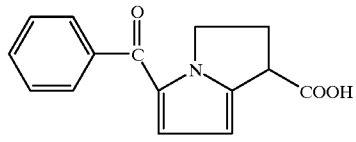
32. The dosage form of claim **31** consisting essentially of an aqueous solution of ketorolac tromethamine that optionally contains a chelating agent and optionally a preservative.

33. The dosage form of claim **27**, wherein said amount of ketorolac tromethamine is sufficient to generate, upon administration of said dosage from to a human subject, a plasma concentration of 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid within said subject between about 0.3 and 5 mg/liter of plasma.

34. The dosage form of claim **27** that includes an atomizer that administers the liquid nasally in the form of a spray.

35. The liquid dosage form of claim **21**, wherein the active ingredient is the optically active form.

36. A method for the treatment of inflammatory processes and pain of a traumatic or pathologic origin in human, which method comprises the administration by the intranasal route of a dosage form comprising a systemically effective amount of an active ingredient selected from the group consisting of racemic 5-benzoyl-2,3-dihyro-1H-pyrrolizine-1-carboxylic acid, of the formula



optically active forms thereof and pharmaceutically acceptable salts thereof, said dosage form being an intranasally-administrable dosage form that achieves blood levels in a host effective for analgesic or anti-inflammatory use after intranasal administration, wherein the dosage form is free of polymers providing a low viscosity at room temperature but an increased viscosity composition at body temperature.

37. The method of claim **36**, wherein the dosage form is a solution.

38. The method of claim **36**, wherein the dosage form is administered in the form of a spray.

39. The method of claim **36**, wherein said effective amount is within the range of about 5–20% (weight/volume).

40. The method of claim **39**, wherein said effective amount is about 15% (weight/volume).

41. The method of claim **36**, wherein the active ingredient is a pharmaceutically acceptable salt.

42. The method of claim **41**, wherein the active ingredient is ketorolac tromethamine and the diluent is water.

43. The method of claim **42**, wherein the dosage form is a solution.

44. The method of claim **43**, wherein said effective amount is within the range of about 5–20% (weight/volume).

45. The method of claim **44**, wherein said effective amount is about 15% (weight/volume).

46. The method of claim **42**, wherein the dosage form consists essentially of an aqueous solution of ketorolac tromethamine optionally containing at least one additive chosen from a humectant, isotoning agent, antioxidant, buffer, preservative, and chelating agent.

47. The method of claim **46**, wherein the dosage form consists essentially of an aqueous solution of ketorolac tromethamine that optionally comprises a chelating agent and optionally a preservative.

48. The method of claim **42**, wherein the active ingredient is ketorolac tromethamine and the effective amount is sufficient to generate aplasma concentration of 5-benzoyl-2,3-dehydro-1H-pyrolizine-1-carboxylic acid between about 0.3 and 5 mg/liter of plasma.

49. The method of claim **42**, wherein the liquid is administered nasally in the form of a spray.

50. The method of claim **36**, wherein the active ingredient is the optically-active form.

51. An analgesic/anti-inflammatory aqueous solution as an intranasally administrable pharmaceutical dosage form in a bottle suitable for delivering a spray of the solution, which dosage form comprises about 5% to about 20% (weight/volume) ketorolac tromethamine, optionally less than about 0.1% (weight/volume) sodium ethylenediaminetetraacetic acid, and optionally a preservative, wherein the dosage form is free of any polymer providing a low viscosity composition at room temperature but an increased viscosity composition at body temperature.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,333,044 B1
DATED : December 25, 2001
INVENTOR(S) : Giancarlo Santus et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [75], Inventor, change "**Ettore Bilato**, Padua (IT)" to
-- **Ettore Bilato**, Padova (IT) --.
Item [30], **Foreign Application Priority Data**, change
"July 22, 1991 (IT) ..... MI91A2024" to -- July 22, 1991 (IT) ..... MI91A 00 2024 --.

Signed and Sealed this

Eleventh Day of March, 2003

JAMES E. ROGAN
Director of the United States Patent and Trademark Office